

THE ACTION OF PITUITARY EXTRACT

ON URINARY SECRETION

T H E S I S

submitted by

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THE ACTION OF PITUITARY EXTRACT ON URINARY

SECRETION.

Introduction.

Since the researches of Magnus and Sharpey-Schafer in 1901, a large amount of work has been performed upon the different aspects of this subject. In view of this it has been found necessary to depart from the usual custom and distribute the literature in its appropriate place in the text.

The subject has been treated under the following headings:-

- (1) The Action of Pituitary Extract on the Output of Urine in Anaesthetised Animals.
- (2) The Effect of Pituitary Extract upon the Output of Urine in Unanaesthetised Animals.
- (3) The Action of Pituitary Extract upon Absorption of Fluid from the Alimentary Tract.
- (4) The Effect of Pituitary Extract upon a Diuresis produced by Intravenous Administration of Ringer Solution.
- (5) The Action of Pituitary Extract upon Blood Composition.
- (6) The Mechanism involved in the Control of Diuresis by Pituitary Extract.

The Action of Pituitary Extract on the Output
of Urine in Anaesthetised Animals.

The first work upon this subject was communicated by Magnus and Schafer in 1901 (1). In experiments on dogs they showed that saline extracts of the pituitary gland, when injected intravenously, produced a transitory rise in blood pressure, accompanied after a short period of latency by a long continued expansion of the kidney and a decided diuresis. The rise in the blood pressure lasted as a rule only a few minutes, while the flow of urine reached its maximum in about fifteen minutes, but at the end of thirty minutes was frequently double the original amount. At first the increase of kidney volume and the increased flow of urine were concomitant: the expansion, however, in some experiments continued after the diuresis had ceased.

In 1906 Schafer and Herring⁽²⁾ made a further contribution to the subject. They showed that a second injection of pituitary extract not infrequently produced no rise but sometimes a fall in blood pressure; in spite of this a diuresis usually resulted.

Further, they found that when extracts of the infundibular portion of the pituitary gland were treated with peptic digestive fluid or hydrogen peroxide, they were deprived of their action on the blood/

blood pressure, but still retained their diuretic action. Occasionally, especially with large doses of the extract, the diuretic effect failed to show itself; this was attributed to vasoconstriction of the renal vessels.

Schafer (4) stated his views on the subject as follows: "The increased secretion (of urine) may be in part brought about by the increased flow of blood through the kidney vessels, due to the circumstance that they undergo dilatation, while all the other systemic arteries are contracting, but that it is to a certain extent caused by a specific effect of one of the pituitary autacoids is probable from the fact that it may occur in the absence of any obvious arterial change". He holds that there is a direct chemical excitation of the renal cells by the autacid, similar to the action of secretion on the pancreatic cells.

In 1909, Halliburton, Candler and Sikes (3) reported that extracts of the whole gland caused an increased output of urine in cats, accompanied by a rise of blood pressure and increased kidney volume. Anterior lobe extracts produced no rise in blood pressure, no alteration in kidney volume and no diuresis.

In 1913, Herring (5) stated that the diuretic effect/

effect of the posterior lobe extracts could be demonstrated in all species of animals and that the extracts from the Pars Intermedia and anterior lobe did not possess this power.

In the same year Hoskins and Means (6), working on dogs anaesthetised with urethane and ether, investigated the relationship between pulse pressure and diuresis after the administration of pituitary extract. In practically all their experiments they obtained a diuresis; sometimes, however, the onset was delayed for two or three minutes. They found no constant relationship between pituitary diuresis and either systolic or pulse pressure or a ratio between them. In conclusion they agreed with Schafer and Herring that the primary effect of pituitary extract was upon the renal cells.

King and Stoland (7) performed a series of experiments upon dogs under anaesthesia; urine flow, kidney volume, and blood pressure were recorded. Commercial pituitary extract was used. After an intravenous injection of pituitary extract they found that a latent period of about five seconds occurred; this was followed by a rather abrupt rise of the systemic blood pressure and a decrease of kidney volume. The constriction of the kidney was followed by a gradual dilatation and a diuresis lasting about twenty minutes. They were unable to obtain a diuresis without a dilatation of the kidney, and considered that/

that the vascular changes were sufficient to account for it.

Knowlton and Silverman (8) investigated the action of commercial pituitary extract on the oxygen consumption of the kidney in cats. The renal blood flow was measured by the Barcroft and Brodie method (9), which consists in diverting the blood from the renal vein into a cannula of known capacity; if the time taken for the cannula to fill is measured with a stop watch, the renal blood flow per minute can be calculated.

They found that increased renal blood flow was a constant accompaniment of the diuresis which resulted from the administration of pituitary extract, and that in a general way the two effects ran parallel to one another. They also state "that in no successfully completed experiment was there evidence that pituitary extract caused increased work on the part of the renal cells as measured by the oxygen consumption." On the basis that stimulation means increased activity and this in turn means increased metabolism, they argue that stimulation of the renal cells does not occur and that the diuresis is purely physical.

Cushny and Lambie (10) in 1921 reported that intravenous injection of pituitary extract was followed in every experiment by a sharp rise in the blood pressure and a considerable acceleration of the/

the blood flow through the kidney persisting for 15 - 25 minutes. The blood flow was measured by a modification of the Barcroft and Brodie method. In some experiments the increased renal blood flow and the raised blood pressure were unaccompanied by an increased flow of urine. When a diuresis did occur, however, it ran almost parallel to the renal blood flow; in view of this the authors considered that the diuresis resulted from increased blood flow through the kidney rather than specific stimulation of the secretory cells.

In 1922, Richards and Plant (21) found that under minute doses of pituitrin, a diuresis resulted and the kidney volume was increased, but the renal blood flow was diminished. They concluded that these results were produced by a slight degree of constriction of the efferent vessels with consequent increase of glomerular pressure.

In 1924, Abel and Rouiller (23), working with an extract of the posterior lobe of the pituitary body which had been converted into the tartrate, reported that a marked diuresis resulted from its administration to anaesthetised rabbits; this was preceded by a cessation of urinary flow for three to eight minutes.

In the same year, Konrad Fromherz (11) reported that he obtained a diuresis in anaesthetised rabbits and dogs from intravenous injection of hypophysin; this effect was usually preceded by a temporary cessation/

cessation of the urinary output. In a further series of experiments he produced a diuresis in rabbits by continuous administration intravenously of 0.9% saline solution; 5 c.c. being given in each period of ten minutes. He then added hypophysin to the saline solution in the proportion of 1:30, and continued the intravenous administration at the same rate as before; as a result of this procedure, the urinary flow became greatly reduced in amount and remained so throughout the administration.

It will be noticed that with the exception of the last series of experiments all the authorities alluded to above observed a diuresis in the majority of experiments after the intravenous administration of pituitary extract in anaesthetised animals. In view of this it seemed desirable that Fromherz's experiments should be repeated.

In all my experiments I have used a preparation of mammalian (ox) pituitary (posterior lobe) for which I am indebted to Dr Hogben and Mr Schlapp of the Physiological Department of Edinburgh University. (30) (Scheme 6)
Extracts of this preparation produced a purely pressor effect. A fresh extract was prepared for each experiment. 5 mg. of this dried substance, extracted with 2 c.c. of 0.9% saline solution, was the dose used except where otherwise stated. This has been referred to in the text as "5 mg. of Pituitary Extract".

Experiment I. /

Experiment I.

A cat, weighing 2.800 grams was anaesthetised with 3.5 c.c. paraldehyde.

Dissection - An incision was made in the neck and cannulae inserted into the trachea, jugular vein, and carotid artery. The bladder was exposed through a small incision in the lower part of the abdomen and a cannula was put in as close to the base of the bladder as possible.

At 11.50 continuous intravenous administration of 0.9% saline solution, warmed to body temperature, was commenced; for this purpose a burette was adjusted to run in 5 c.c. every 10 minutes. The rate of flow was checked each minute with a stop-watch.

<u>Time</u>		<u>Administration</u>	<u>B.P.</u>	<u>Urine</u>
11.50 - 12	(10 mins)	5 c.c.	138 mm Hg.	.4 c.c.
12 - 12.10	"	5 c.c.		.6
12.10 - 12.20	"	5 c.c.	120 "	.7
12.20 - 12.30	"	5 c.c.		1.2
12.30 - 12.40	"	5 c.c.	120 "	1.5

To 48 c.c. of saline solution, 5 mg. of pituitary extract were added (2 c.c.) and the administration resumed at the same rate.

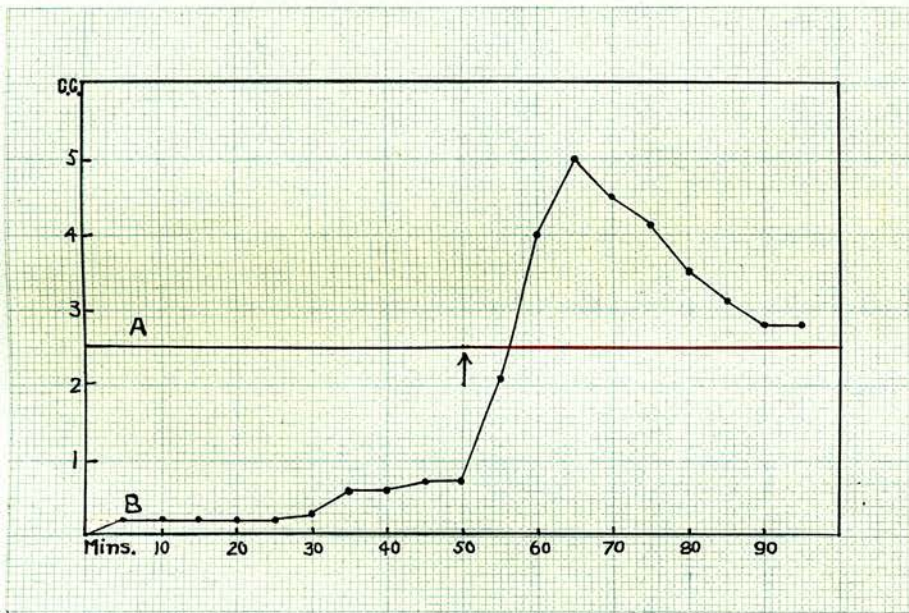
N.B. As the quantity of urine was greater, five minute specimens were taken.

12.44 /

Experiment I contd.

<u>Time</u>	<u>Administration</u>	<u>B.P.</u>	<u>Urine</u>
12.44 - 12.49 (5 mins)	2.5 c.c.	120 mm Hg.	2.1 c.c.
12.49 - 12.54 "	2.5 c.c.		4.1
12.54 - 12.59 "	2.5 c.c.	126 "	5.0
12.59 - 1.4 "	2.5 c.c.		4.5
1.5 - 1.10 "	2.5 c.c.	126 "	4.2
1.10 - 1.15 "	2.5 c.c.		3.5
1.16 - 1.21 "	2.5 c.c.		3.2
1.21 - 1.26 "	2.5 c.c.	120 "	2.8
1.26 - 1.31 "	2.5		2.8

Cat - 2.800 grams. Paraldehyde anaesthesia - 3.5c.c.



Ordinate = c.c. in each period of 5 minutes

Abscissa = Time in minutes

A = Intravenous administration - c.c. per 5 minutes.

Black line = saline administration

Red line = saline + 5.0 mg. pituitary extract

B = Urine in c.c. per 5 minutes

In this experiment the blood pressure fell 18 mm. after the first 20 minutes and thereafter varied very little; the urinary flow, on the other hand, increased enormously immediately after pituitary extract was added to the saline solution and reached a maximum in 15 minutes, but at the end of 45 minutes, it was still four times greater than before the extract was added.

The first half of the experiment lasted 50 minutes and in that time 25 c.c. of saline solution were administered and 4.4 c.c. of urine passed; the second half lasted 45 minutes, 22.5 c.c. of saline plus 2.5 mg. of pituitary extract were administered and 36.5 c.c. of urine excreted.

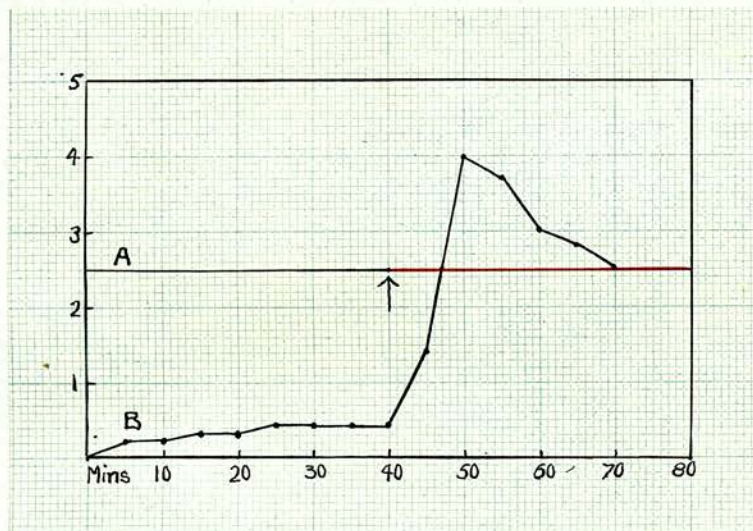
Obviously diuresis could not continue at this rate for a prolonged period. It is not surprising therefore that the output of urine gradually became less.

Experiment II.

Cat - 2.200 grams. Paraldehyde anaesthesia - 3 c.c.

Chart II /

Experiment II.



Ordinate = c.c. in each period of 5 minutes

Abscissa = Time in minutes

A = Intravenous administration - c.c. per 5 minutes

Black line = saline administration

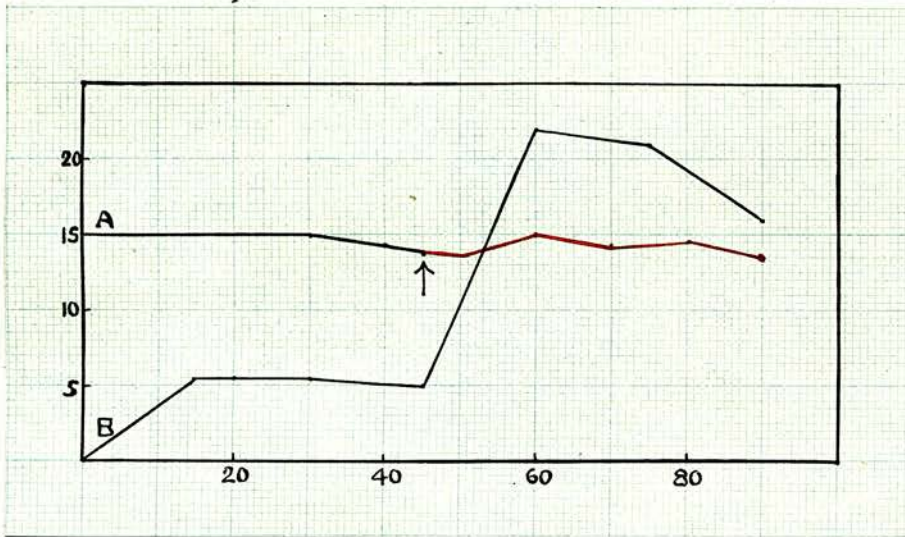
Red line = saline + 2.5 mg. pituitary extract.

B = Urine in c.c. per 5 minutes.

Experiment III. /

Experiment III.

Cat - 3000 grams. Urethane - 3 grams.



Ordinate = c.c. in each period of 15 minutes

Abscissa = Time in minutes

A = Intravenous administration

Black line = saline administration

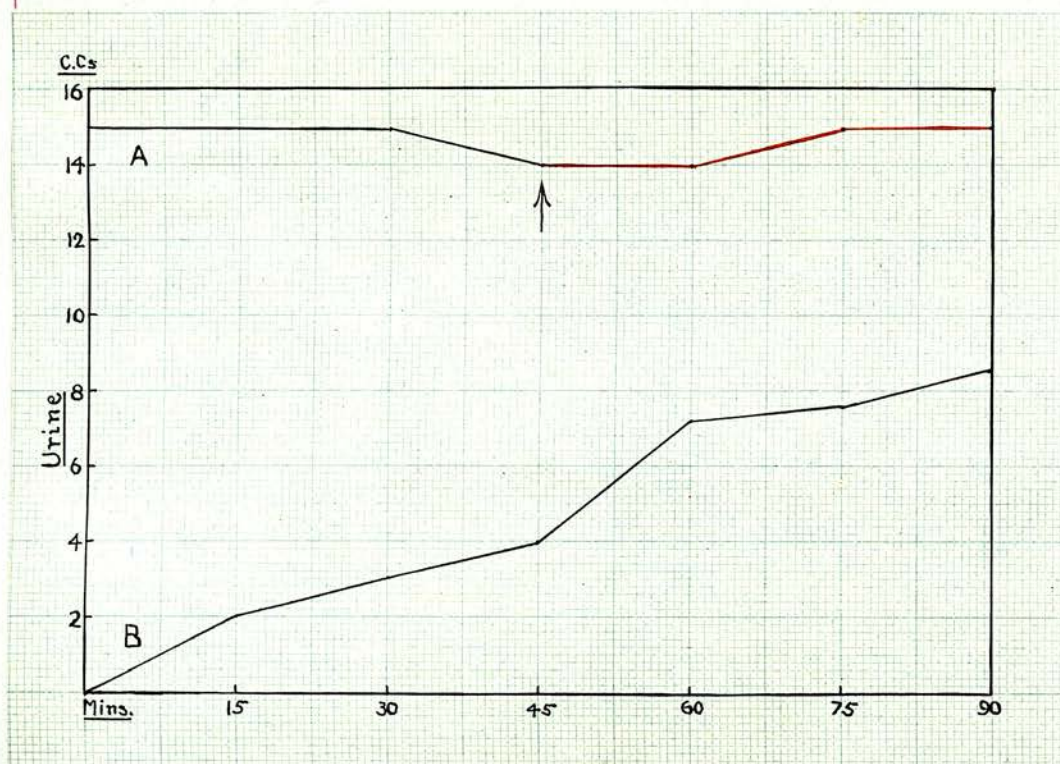
Red line = saline + 5 mg. pituitary extract

B = Urine in c.c. per 15 minutes

Experiment IV. /

Experiment IV.

Cat - 2900 grams. Urethane - 3 grams.



Ordinate = c.c. in each period of 15 minutes

Abscissa = Time in minutes

A = Intravenous administration.

Black line = saline administration

Red line = saline administration +
5 mg. pituitary extract.

In experiments III and IV the rate of the saline administration intravenously was 1 c.c. each minute. In each experiment a marked increase in the output of urine resulted from the addition of pituitary extract to the transfused solution.

Kidney Perfusion Experiments.

In 1909 Dale (12) reported the results of kidney perfusion experiments; the outflow of the vein was recorded by a drop recorder. A diminution in the outflow from the renal vein was observed after the addition of pituitary extract.

In 1912 Pentimalli and Quercia (14) showed that pituitary extract diminished the flow from ureter and renal vein.

In 1914 Gabriels (13) reported that he obtained increased flow from the ureter after pituitary extract had been added to the perfusion solution, and that this was not associated with vaso-dilation. In conclusion he agreed with Schafer and Herring that pituitary extract stimulated the renal cells.

The Effect of Pituitary Extract upon the Output of
Urine in Unanaesthetised Animals.

A. The Action of Pituitary Extract upon diuresis produced by the administration of water by the mouth.

Since 1913 many cases of Diabetes Insipidus have been recorded in which the administration of extracts of the posterior lobe of the pituitary gland have been effective in decreasing the amount of urine excreted. As a result of these observations many experiments have been carried out on unanaesthetised animals.

In 1914 Römer (28) reported that the flow of urine ^{is} ~~was~~ decreased after the administration of pituitary extract in rabbits and cats catheterised every hour (quoted by Motzfeldt).

In 1917 Motzfeldt (16) published the results of extensive experimentation carried out chiefly on male rabbits.

In one series of experiments the animals were given 150-200 c.c. of water by the stomach tube; catheterisation was carried out every half hour until the diuresis subsided. As a rule the polyuria commenced within one to two hours and subsided within five to six hours; the curves, however, were subject to considerable variation. When pituitary extract (commercial) was injected subcutaneously at the beginning/

beginning of the experiment, the diuresis was delayed for five to six hours; if it was administered after the diuresis had commenced, the output of urine subsided for a similar length of time; the effect of the injection was little marked during the first 30 minutes and reached a maximum in two hours. He stated that he obtained this effect in all the experiments carried out under these conditions. Intravenous injection of pituitary extract gave similar results, but the action was usually more rapid in its onset; oral administration also produced a delay in diuresis, but the onset was slow.

In 1918 Rees (17) repeated Motzfeldt's experiments on rabbits, using the same technique, and confirmed the antidiuretic action of pituitary extract. He also reported that the total output of urine in twenty-four hours was unaffected by one daily injection of the extract subcutaneously.

In 1921 Priestley (20) recorded results of similar experiments upon human beings; he found that the diuresis which would normally result from the drinking of two litres of distilled water was delayed for four to six hours after pituitary extract had been administered intramuscularly (commercial extract used - 1 c.c. dose). (u)

In 1923 Fromherz working on dogs confirmed the results of Motzfeldt with regard to subcutaneous injection/

injection of pituitary extract, but maintained that under certain circumstances a diuresis and not an antidiuresis resulted.

In control experiments he showed that if 1000 c.c. of water were administered to 10 kilo. dogs in two doses at an hour interval, a diuresis was produced which reached a maximum in four hours; if, however, an injection of pituitary extract was given subcutaneously two hours before the administration of the fluid, the diuresis reached its maximum in three hours. He drew attention to this as an example of the diuretic action of the extract; it must be remembered, however, that for the two hours prior to the administration of water by the mouth, the pituitary extract had been exerting its antidiuretic effect, so that the urinary flow was reduced to very small dimensions, the remainder of the fluid being retained. At the end of four hours the effect of the extract had passed off and the animal was able to excrete not only the water given by the mouth, but also the retained fluid.

When pituitary extract was administered intravenously, he found that a diuresis and not an antidiuresis resulted; it is worthy of note, however, that Motzfeldt (16) and Molitor and Pick (22) both obtained an antidiuresis by this method.

In 1924 Molitor and Pick (22), working on dogs, confirmed the findings on the antidiuretic action of/
of/

of pituitary extract both by subcutaneous and intravenous administration. This effect was also obtained in a dog with ^{an}Eck Fistula.

The following experiments are confirmatory.

In order to facilitate catheterisation female dogs were used. The perineum of each animal was incised and the mucous membrane sutured to the cut skin surface. The animals were given two meals a day, consisting of meat and bread; one at 10 a.m. and one at 5 p.m. Unlimited fluids were allowed. No food, either fluid or solid, was given for 14 hours before an experiment.

Method.

After the animal had been catheterised 250 c.c. of water were administered by stomach tube and the urine was collected by catheter every half-hour thereafter, until the diuresis subsided.

The experiment was repeated, under the same conditions, a few days later, but with the addition of a subcutaneous injection of 5 mg. of dried posterior lobe extracted in 2 c.c. of saline solution.

Experiment V. /

Experiment V. Dog 12.5 kg.

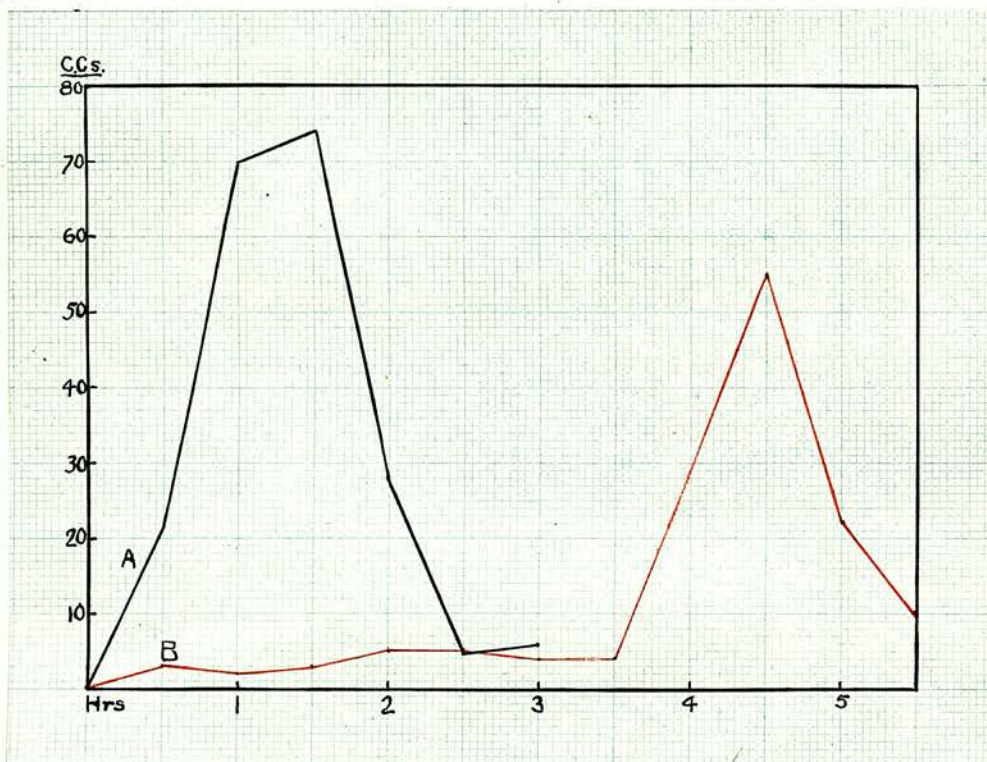
(A) Control experiment (normal diuresis curve).

11.10	Animal catheterised	
11.20	250 c.c. water by stomach tube	
11.50	Animal catheterised -	22 c.c.
12.20	"	70 c.c.
12.50	"	74 c.c.
1.20	"	28 c.c.
1.50	"	5 c.c.
2.50	"	6 c.c.

(B) Experiment repeated under same conditions but
the administration of 5 mg. of pituitary extract
(2 c.c.) subcutaneously.

10.30	Animal catheterised	
10.40	250 c.c. water by stomach tube	
10.45	5 mg. pituitary extract subcutaneously	
11.10	Animal catheterised -	3 c.c.
11.40	"	2 c.c.
12.10	"	3 c.c.
12.40	"	5 c.c.
1.10	"	5 c.c.
2.10	"	8 (= 4 c.c. per $\frac{1}{2}$ hour)
2.40	"	30
3.10	"	55 c.c.
3.40	"	22.5 c.c.
4.10	"	10 c.c.

Chart V.



Ordinate = c.c. of urine passed in each half hour period.

Abscissa = Time in Hours

Curve A = Control diuresis

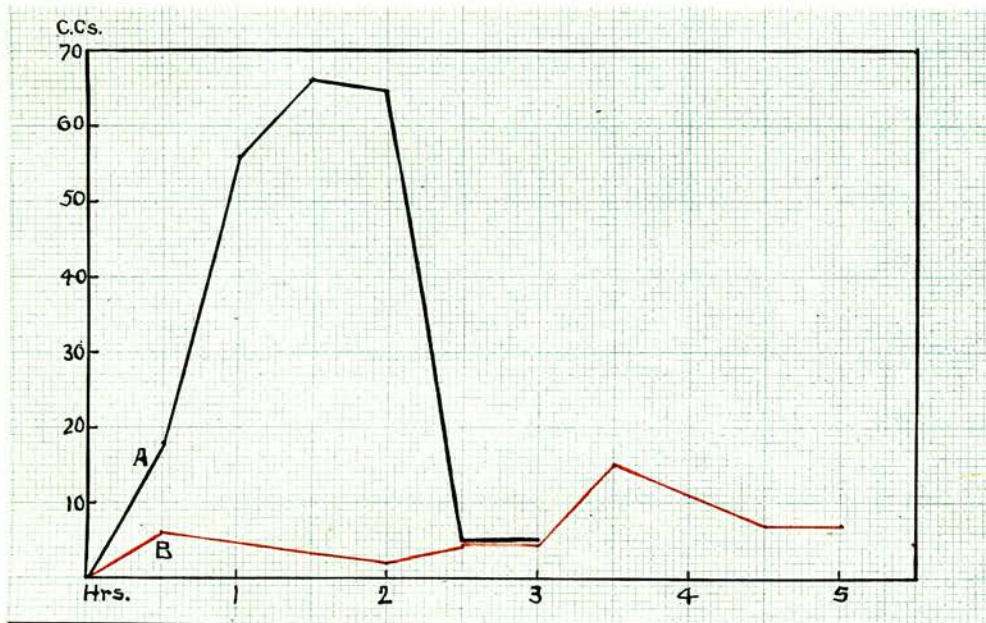
Curve B
(red) = Effect of pituitary extract upon the diuresis curve.

250 c.c. of water were administered by stomach tube at zero in each experiment.

Experiment VI. /

Experiment VI.

Dog - 12.5 kg.



Ordinate = c.c. of urine passed in each half-hour period.

Abscissa = Time in hours

Curve A = Control diuresis

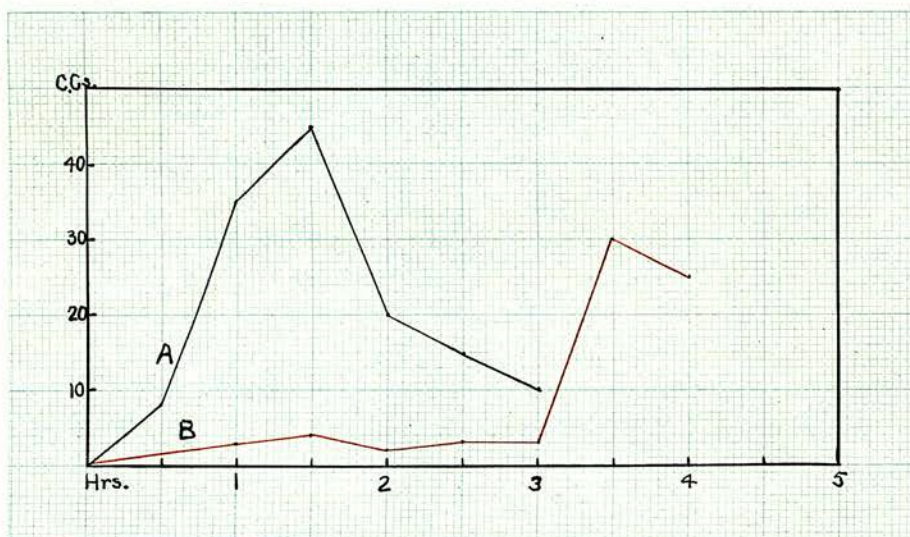
Curve B (red) = Effect of pituitary extract upon the diuresis curve. *5 m.g. Pituitary extract at zero.*

250 c.c. of water were administered by stomach tube at zero in each experiment.

Experiment VII. /

Experiment VII.

Dog - 12.5 kg.



Ordinate = c.c. of urine passed in each half-hour period.

Abscissa = Time in hours

Curve A = Control diuresis

Curve B = Effect of pituitary extract upon the diuresis curve.
(red)

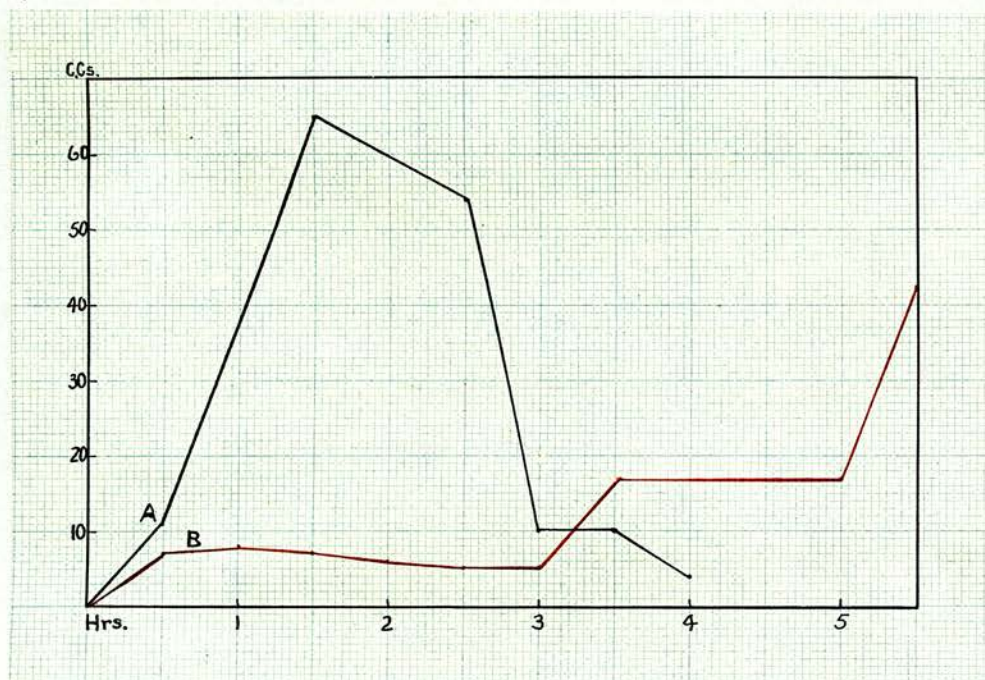
5 m.g. of Pituitary Extract at Zero - subcutaneous.

250 c.c. of water were administered by stomach tube at zero in each experiment.

Experiment VIII./

Experiment VIII.

Dog - 14.5 kg.



Ordinate = c.c. of urine passed in each half-hour period.

Abscissa = Time in hours

Curve A = Control diuresis

Curve B (red) = Effect of pituitary extract upon the diuresis curve.

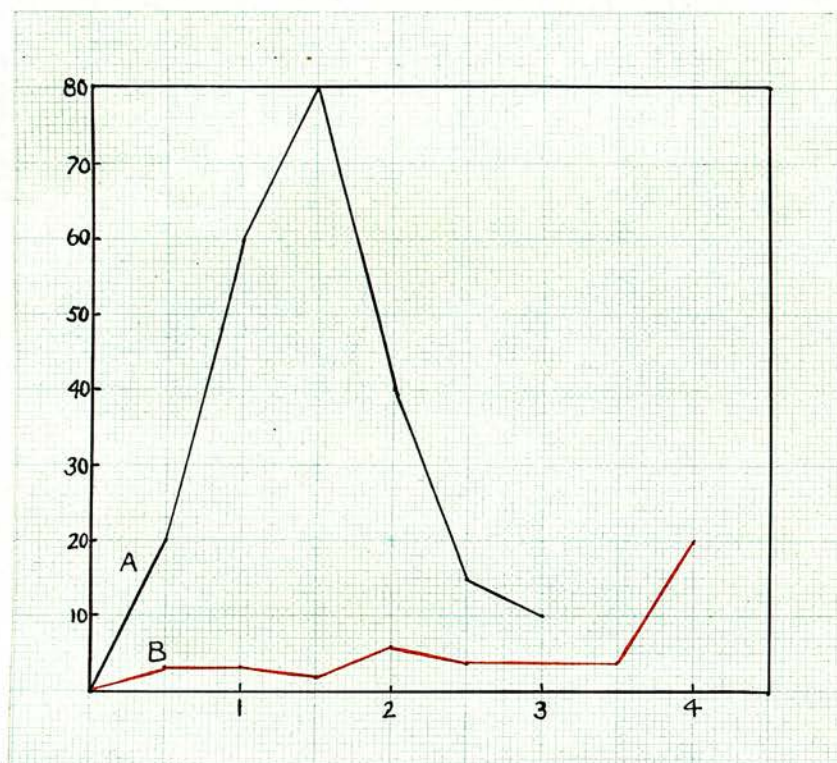
5 m.g. of Pituitary extract at zero - simultaneous.

250 c.c. of water were administered by stomach tube at zero in each experiment.

Experiment IX. /

Experiment IX.

Dog - 15.5 kg.



Ordinate = c.c. of urine passed in each half-hour period.

Abcissa = Time in hours

Curve A = Control diuresis

Curve B = Effect of pituitary extract upon the diuresis (red)

5 m.g. of Pituitary Extract at zero - subcutaneous.

250 c.c. of water were administered by stomach tube at zero in each experiment.

In the normal curves the diuresis usually commenced within half an hour of the administration of water by the mouth, and rapidly increased, reaching a/

a maximum in all experiments within two hours, and falling to an output of 10 c.c. per half hour three hours after the fluid was given.

It will be noted that the height of the curve varied slightly in each experiment, but the form was very constant. When pituitary extract was administered subcutaneously at the beginning of the experiment the diuresis curve was profoundly altered. For a period varying from 3-3 $\frac{1}{2}$ hours after the water was given by the mouth, the output of urine per half hour was under 10 c.c.; then a diuresis occurred which was usually smaller than the control diuresis. The output varied considerably in different experiments, but in all without exception a delay in the onset of diuresis occurred for at least three hours.

Conclusion.

Pituitary extract administered subcutaneously delays the diuresis which would normally result from the administration of water by the mouth for a period of at least three hours.

B. The Action of Pituitary Extract upon a Diuresis
produced by the Administration of Saline
Solution by the Mouth.

Historical.

In 1917 Motzfeldt (16) reported that the usual effective dose of pituitary extract did not influence the polyuria resulting from the administration of 40 c.c. of a 10% sodium chloride solution by stomach-tube in rabbits.

In 1923 Fromherz made the observation that if the animal was given sodium chloride beyond physiological limits, no delay in the diuresis occurred after pituitary extract administration.

In 1924 Molitor and Pick made a similar observation.

The observations recorded above were performed with quantities of concentrated saline solution.

I have carried out observations using 0.9% saline solution. The technique of the experiment was identical to that described for the water diuresis.

Experiment X. /

Experiment X.

Dog - 12.5 kg.

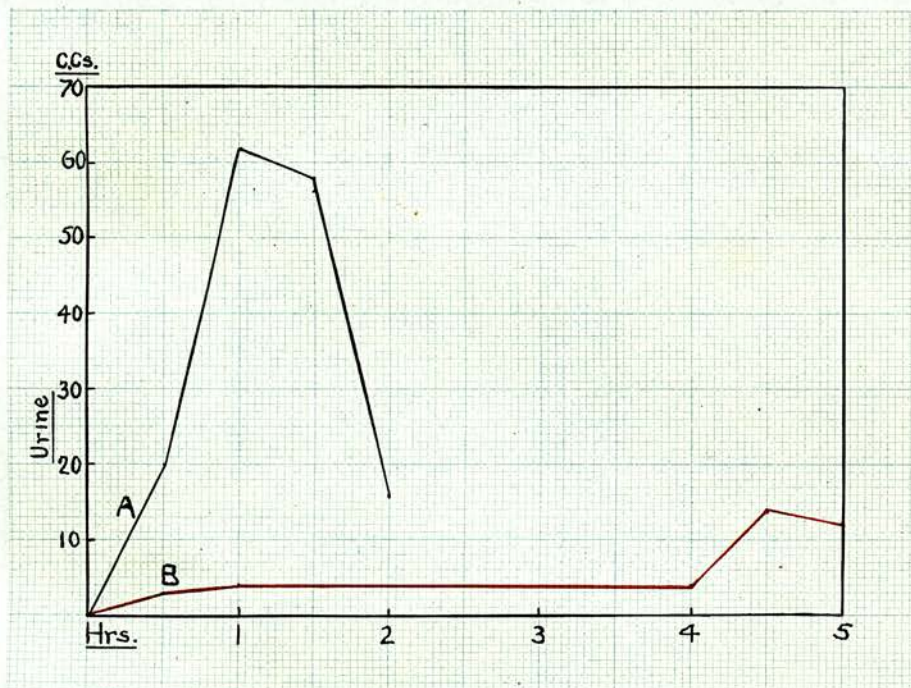
(A) Control Experiment (without administration of
pituitary extract)

11.10 a.m.	Animal catheterised	
11.20 "	210 c.c. saline solution (0.9%) by stomach tube	
11.40 "	Animal catheterised - 20 c.c. urine	
12.10 p.m.	"	62 c.c. "
12.40 "	"	59 c.c. "
1.10 "	"	16 c.c. "

(B.) Experiment repeated with pituitary extract
administration.

10.20 a.m.	Animal catheterised	
10.25 "	5 mg. pituitary extract subcutaneously 210 c.c. of 0.9% saline solution by stomach tube	
10.50 "	Animal catheterised - 3 c.c. urine	
11.20 "	"	4 c.c. "
11.50 "	"	4 c.c. "
12.20 p.m.	"	4 c.c. "
12.50 "	"	4 c.c. "
1.20 "	"	3 c.c. "
1.50 "	"	3 c.c. "
2.20 "	"	4 c.c. "
2.50 "	"	14 c.c. "
3.20 "	"	12 c.c. "

Chart X.



Ordinate = c.c. of urine passed in each half-hour period.

Abscissa = Time in hours

Curve A = Control diuresis

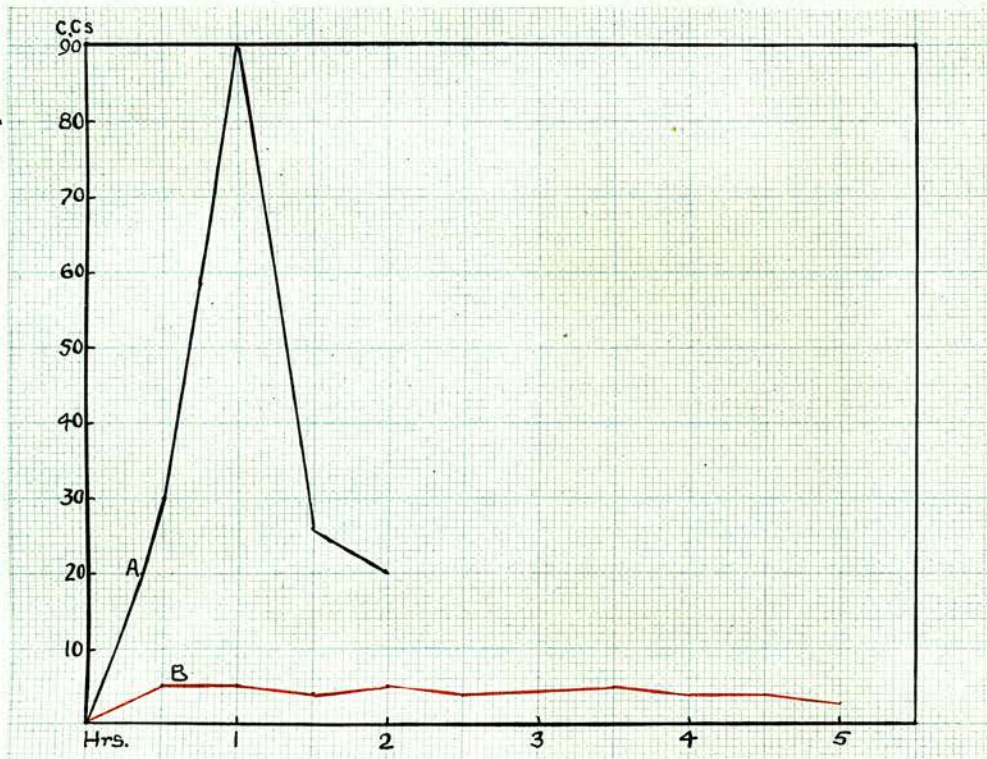
Curve B = Effect of pituitary extract upon the
(red) diuresis.
5 m.g. Pituitary Extract Subcutaneously at Zero.

210 c.c. of 0.9% saline solution were administered by stomach tube at zero in each experiment.

Experiment XI. /

Experiment XI.

Dog - 15.5 kg.



Ordinate = c.c. of urine passed in each half-hour period.

Abscissa = Time in hours.

Curve A = Control diuresis.

Curve B = Effect of pituitary extract upon the diuresis.
(red)

5 m.g. Pituitary Extract subcutaneous at zero

210 c.c. of 0.9% saline solution were administered by stomach tube at zero in each experiment.

In /

In the control experiments (without the administration of pituitary extract) the output of urine rose more rapidly than in the case of the water diuresis and reached a maximum in both experiments in one hour. In two hours the output had fallen to 20 c.c. per half-hour. After the administration of pituitary extract, the diuresis curve was greatly altered. In experiment I. the output of urine per half-hour did not rise above 4 c.c. for 4 hours after the saline solution was given; then a very small diuresis occurred.

In experiment II. the output did not rise above 5 c.c. per half-hour during the whole five hours of the experiment. In both experiments, the period of delay in the onset of diuresis was greater than in the experiments in which water was given by the mouth (see page 19).

Conclusions.

- I. Pituitary extract delays the diuresis which would normally result from the administration of normal saline solution by the mouth.
- II. The period of delay is more prolonged than with a water diuresis.

C. The Action of Pituitary Extract upon a diuresis
produced by the Administration of Urea Solution
by the mouth.

The same technique and preparation was adhered to.

A 5% urea solution was used.

Experiment XII.

Dog - 12.5 kg.

(A.) Control Experiment.

10.30 a.m.	Animal catheterised		
10.35 "	220 c.c. of 5% urea solution administered by stomach tube		
11.0 "	Animal catheterised -	37 c.c.	urine
11.30 "	"	95 c.c.	"
12.0 p.m.	"	36 c.c.	"
12.30 "	"	27 c.c.	"
1.0 "		10 c.c.	"

(B.) Experiment repeated with the administration of pituitary extract.

10.40 /

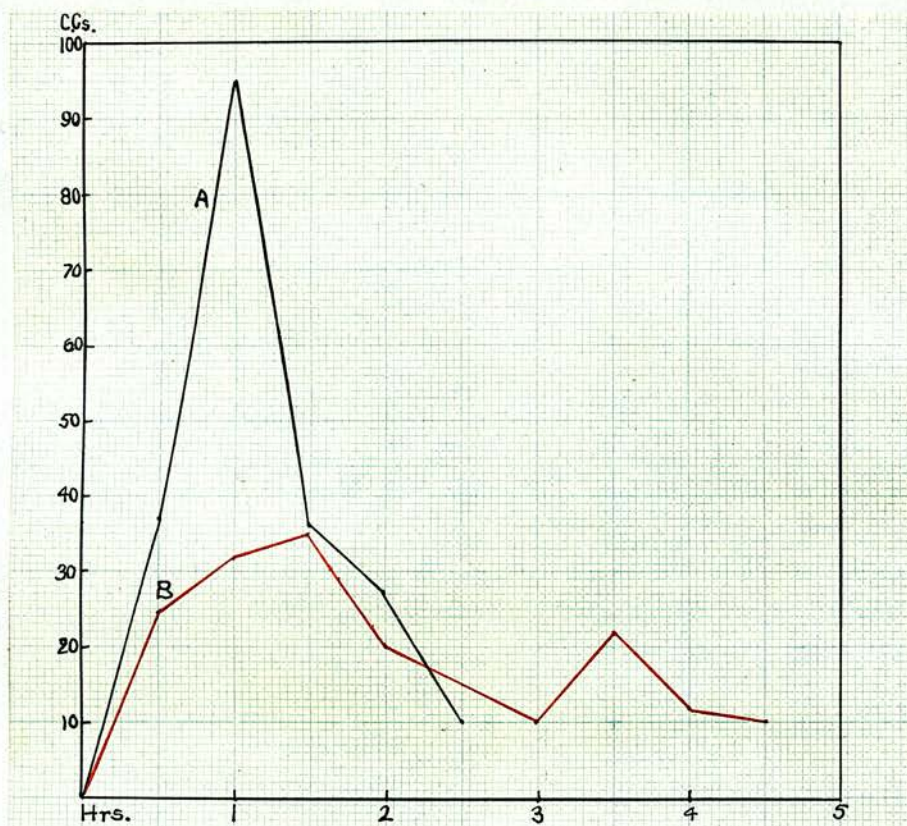
Experiment XII contd.

(B.) Experiment repeated with the administration of
pituitary extract.

10.40 a.m.	Animal catheterised		
10.43 "	5 m.g. pituitary extract in 2 c.c. saline solution	subcutaneously	
10.45 "	220 c.c. 5% urea solution	by stomach tube.	
11.15 "	Animal catheterised -	24 c.c. urine	
11.45 "	"	32 c.c.	"
12.15 p.m.	"	35 c.c.	"
12.45 "	"	20 c.c.	"
1.15 "	"	15 c.c.	"
2.15 "	" 20 c.c. =	10 c.c. per half-hour	
2.45 "	"	22 c.c. urine	
3.15 "	"	12 "	
3.45 "	"	10 c.c.	"

Chart XII. /

Chart XII.



Ordinate = c.c. of urine passed in each half-hour period.

Abscissa = Time in hours

Curve A = Control diuresis.

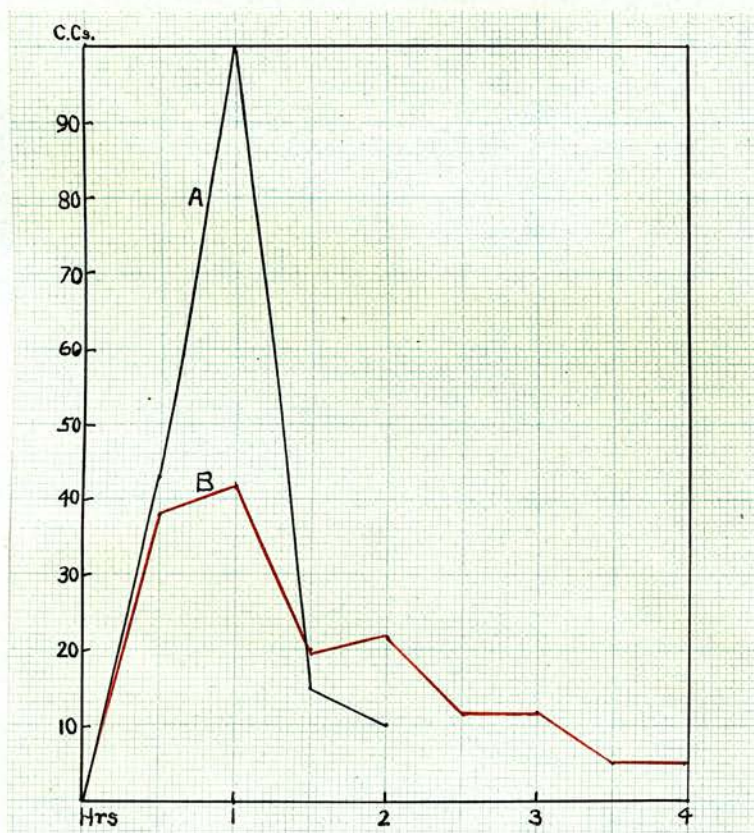
Curve B (red) = Effect of pituitary extract upon the diuresis.

220 c.c. of 5% urea solution were administered by stomach tube at zero in each experiment.

Experiment XIII. /

Experiment XIII.

Dog - 10 kg.



Ordinate = c.c. of urine passed in each half-hour period.

Abscissa = Time in hours

Curve A = Control diuresis.

Curve B (red) = Effect of pituitary extract upon the diuresis.

5 m.g. Pituitary Extract Subcutaneous, at zero.

220 c.c. of 5% urea solution were administered by stomach tube at zero in each experiment.,

In /

In the control experiments the diuresis commenced within half an hour of the administration of urea solution by the mouth, reached a maximum in one hour, and subsided in two hours.

When pituitary extract was administered, no delay in the onset of diuresis occurred in either experiments; but the half-hourly output was much smaller and the diuresis more prolonged than in the control experiments.

Conclusion.

Pituitary extract when administered subcutaneously prolongs a diuresis produced by the oral administration of 220 c.c. of 5% urea solution, but does not delay its onset.

The Action of Pituitary Extract upon Absorption of
Fluid from the Alimentary Tract.

The action of pituitary extract on the urinary output in intact animals has been investigated almost exclusively upon a diuresis produced by the administration of water by the mouth. In these experiments a delay in the diuresis has invariably resulted. As a delay in absorption of fluid from the alimentary tract might be expected to cause a delay in the onset of diuresis, it seemed necessary that the action of pituitary extract upon absorption should be investigated.

Maurice Rees (17), using cats anaesthetised with urethane, investigated this problem as follows:-

Loops of small intestine were tied off and 30 c.c. of water were introduced into each; absorption was allowed to proceed for one hour, then the contents were measured. The experiment was immediately repeated upon the same animal after the administration of pituitary extract.

He found that pituitary extract greatly delayed absorption and concluded that the delay in diuresis in unanaesthetised animals was, in part at least, due to this cause.

The same author, in a second contribution published in 1920 (18) gave the results of further experiments/

experiments on anaesthetised dogs and cats and on decerebrated dogs. The method was very similar to that described above.

In practically all the animals a delay in the absorption of fluid from the small intestine occurred after the administration of pituitary extract subcutaneously; the decrease in the absorption rate in these experiments, however, was much less than that recorded in the first series (1918) and he concluded that the delay in absorption did not seem to be sufficient, in most cases, to account entirely for the delay in the excretion of water from the kidney which has been known to result from pituitary injection.

These experiments do not furnish satisfactory evidence for two reasons:

(1) They were performed upon anaesthetised and decerebrate animals, and it has to be assumed that pituitary extract will act in the same way in unanaesthetised intact animals, since it is only in the latter that the antidiuretic action of pituitary extract has been satisfactorily demonstrated.

(2) The handling, tying off, and exposure of loops of intestine must complicate the result.

In the experiments recorded below, I have attempted to ascertain on unanaesthetised intact animals/

animals whether or not absorption from the alimentary tract is sufficiently delayed after the administration of pituitary extract to account for the delay in diuresis.

Two preliminary experiments were performed to ascertain if absorption was completely delayed for a period after administration of pituitary extract. For this purpose water darkly stained with indigo-carmin was given by the mouth, and observations made upon:

- (1) the latent period before the dye appeared in the urine
- (2) the amount of urine passed.

Experiment I.

Dog - 12.5 kg.

(A) Control experiment - no pituitary extract administered.

11.5	a.m.	Animal catheterised		
11.10	"	250 c.c. of water, darkly stained with indigo-carmin given by stomach tube		
11.20	"	Animal catheterised -	3 c.c.	urine
11.30	"	"	5 c.c.	"
12.0		"	30 c.c.	"
12.30	p.m.	"	40 c.c.	"
1.0	"	"	20 c.c.	"
1.30	"	"	15	"
2.0	"	"	10	"

The/

The first specimen of urine obtained ten minutes after the administration of fluid by the mouth had a definite bluish colour. The diuresis curve was normal.

(B) Experiment repeated under the same conditions,
but with the administration of pituitary extract.

12.0	5 mg. pituitary extract in 1 cc. saline solution subcutaneously.	
12.5 p.m.	Animal catheterised	
12.10 "	250 c.c. of coloured water by stomach tube	
12.20 "	Animal catheterised -	no urine obtained
12.30 "	"	1 c.c. urine
1.0 "	"	3 c.c. "
1.30 "	"	4 c.c. "
2.0 "	"	2 c.c. "
2.30 "	"	3 c.c. "
3.0 "	"	3 c.c. "
3.30 "	"	30 c.c. "
4.0 "	"	25 c.c. "

No urine could be obtained until 20 minutes after the oral administration; this specimen was darkly stained with dye. A definite delay in the diuresis occurred. The experiment was repeated on a second dog with similar results.

In the control experiment the dye appeared in 12 minutes. After the administration of pituitary extract/

extract the dye appeared in the first specimen of urine, obtained 15 minutes after the water was given by the mouth.

The only inference that can be drawn from these experiments is that absorption of the dye from the alimentary tract commences very soon after its administration by the mouth in both the control and the experiment in which pituitary extract was given.

The experiment was not, however, quantitative.

In order to obtain an exact idea of the duration of time necessary for absorption of the fluid from the alimentary tract, after the administration of pituitary extract, the following experiments were undertaken:

Experiment I.

A cat weighing 3200 grams was deprived of fluid overnight: at 10 a.m. 5 mg. of pituitary extract (2 c.c.) were administered subcutaneously: at 10.5 224 c.c. of water were given by the mouth (70 c.c. per kilo.) and the animal was placed in a small cage with a drain to collect the urine. At 12.20, two and a half hours after the fluid was given, the animal was killed under chloroform anaesthesia. No motion of the bowels occurred during the experiment: the stomach contained 4 c.c. of fluid: the intestine contained only a very small quantity of semi-solid faeces.

Water/

Water administered by stomach tube	-	224 c.c.
Water obtained from stomach and intestines, not more than	-	<u>10 c.c.</u>
Fluid absorbed in $2\frac{1}{2}$ hours	=	214 c.c.
Urine passed . . .	-	0
Urine in bladder . . .	-	<u>16 c.c.</u>

Fluid absorbed and not excreted = 198 c.c.

In this experiment only 16 c.c. of urine were excreted in $2\frac{1}{2}$ hours and during the same period at least 214 c.c. of fluid had been absorbed.

It is useful at this stage to compare this result with a control experiment, carried out under the same conditions, but without the administration of pituitary extract.

Experiment II.

Cat - 2300 grams.

10 a.m. 161 c.c. administered by stomach tube (70 c.c. per kilo.)

12.30 p.m. Animal killed by chloroform anaesthesia.

Water administered . . .	161 c.c.
Fluid in stomach and intestines, not more than	<u>10 c.c.</u>
Fluid absorbed. . .	151 c.c.
Urine passed in $2\frac{1}{2}$ hours .	<u>122 c.c.</u>
Fluid absorbed and not excreted . . .	29 c.c.

A comparison of the two results shows that in both experiments practically the whole of the fluid was/

was absorbed from the alimentary canal in $2\frac{1}{2}$ hours: in spite of this fact the diuresis recorded in the control experiment did not appear in the experiment in which pituitary extract was administered.

On these points I submit that the delay in absorption from the alimentary canal, if it occurs after the administration of pituitary extract, is insufficient to account for the delay in diuresis.

Three experiments were carried out using larger quantities of water and extending the observations over a longer period of time.

Experiment III.

A cat weighing 2 kg. received 5 mg. of pituitary extract (2 c.c.) subcutaneously at 9.55: at 10, 11, 12, and 1 o'clock it received 100 c.c. of water by the mouth, total 400 c.c.

The animal was kept in a cage and the urine collected.

At 1 p.m. a second injection of 5 mg. of pituitary extract was given. At 1.30 the animal became drowsy; at first slight lateral swaying movements were noticed, later a definite nodding of the head; the animal gradually became more drowsy and died at 2.30. No convulsions took place. Frothing at the mouth was noticed just before death.

Quantity/

Quantity of fluid administered -	400 c.c.
Fluid in stomach and intestine -	30 c.c.
Fluid in bladder -	0
Urine passed in $4\frac{1}{2}$ hours -	<u>65 c.c.</u>

370 c.c. of water were absorbed and only 65 c.c. of urine passed. 305 c.c. were unaccounted for.

Experiment IV.

Cat - 2.5 kilo.

No fluid was given to the animal overnight.

10 a.m. 5 mg. pituitary extract in 2 c.c. of saline subcutaneously

10.5 " 100 c.c. water by mouth

11. " 100 c.c. "

12. 100 c.c. "

1. p.m. 100 c.c. "

1.5 " 5 mg. pituitary extract subcutaneously (2 c.c.)

3. " Animal killed by ether anaesthesia

Towards the end of the experiment the animal lay still in the cage but did not show such marked symptoms of drowsiness as observed in experiment III.

Quantity of fluid administered -	400 c.c.
Fluid in stomach and intestine -	<u>20 c.c.</u>
Fluid absorbed in 5 hours -	380 c.c.
Urine excreted do. -	<u>108 c.c.</u>
Fluid absorbed and not excreted by kidney -	272 c.c.

The/

The peritoneal and pleural cavities both contained a quantity of free fluid, but there was no oedema of the tissues observed. The urine in the bladder was stained dark brown, due probably to haemolytic changes in the blood, since there was no lesion in the bladder to account for it. The urine passed before death was straw-coloured.

Experiment V.

Dog - 15.5 kg.

The animal was deprived of fluid and food overnight.

10.45 a.m. Animal catheterised

10.50 " 5 mg. pituitary extract in 2 c.c. saline solution subcutaneously

11.0 " 500 c.c. of water administered by stomach tube

12.55 p.m. 800 c.c. of water administered by stomach tube (300 c.c. vomited)

1.0 " Animal catheterised - 90 c.c. urine

1.5 " 5 mg. pituitary extract subcutaneously (2 c.c.)

2.45 " Animal catheterised - 30 c.c. urine

3.0 " Animal killed by chloroform anaesthesia.

No signs of drowsiness or discomfort were present.

Total/

Total fluids administered	-	1300 c.c.
Fluid vomited	-	300 c.c.
Fluid in stomach and intestine		<u>80 c.c.</u>
Fluid absorbed in 4 hours		920 c.c.
Urine passed	-	<u>120 c.c.</u>
Fluid absorbed and not excreted		800 c.c.

A survey of these experiments shows that the intestine is capable of absorbing extremely large quantities of fluid at a fairly rapid rate after the administration of pituitary extract; it is therefore impossible that a delay in diuresis for 3 to $3\frac{1}{2}$ hours can be due to delayed absorption from the alimentary tract.

The Effect of Pituitary Extract upon a Diuresis produced by Intravenous Administration of Ringer Solution.

It has been shown that pituitary extract, whether administered subcutaneously or intravenously, causes a delay in diuresis when water is given by the mouth, and that this delay is not due to delayed absorption from the alimentary tract; in spite of this, in an anaesthetised animal, a diuresis usually results from the intravenous injection of the extract.

It seemed desirable, therefore, that an investigation into the action of pituitary extract upon a diuresis produced by intravenous injection of Ringer solution should be undertaken in unanaesthetised animals.

Method.

In the first experiments (not recorded) an attempt was made to give the injection of Ringer solution through a wide-bore needle by venepuncture. This method proved unsatisfactory, firstly, because a dog's skin is tough and freely moveable, making the puncture of the skin difficult; secondly, it was almost impossible to hold the needle in the vein for a sufficiently long time to give the injection of a large quantity of fluid. Superficial venesection was/

was therefore performed. The animal was laid upon its side and lightly held by two assistants; a vein, in the distal part of one of the hind legs, was selected and the hair removed over a small area; $\frac{1}{2}$ c.c. of 4% novocain solution was injected subcutaneously at the site, and a small incision, $\frac{1}{4}$ " long made. The vein was exposed, clamped proximally and tied distally. A small venous cannula was inserted and tied in. This method has the disadvantage that the vein must be tied at the end of the transfusion; for this reason two experiments only were performed on each animal. The fluid used was sterilised Ringer solution, run in from a burette.

Formula of Ringer solution.

Sodium chloride	-	.9	grams
Potassium chloride	-	.4	"
Calcium chloride	-	.2	"
Sodium bicarbonate	-	.2	"
Distilled water	-	1	litre

In the first two experiments, 120 c.c. of Ringer solution were given intravenously in ten minutes. It was considered that a dog would not remain quiet for a longer period, but this estimate later proved to be incorrect. After the injection the animal was allowed a limited amount of freedom and was catheterised every half hour until the diuresis subsided.

Experiment I. /

Experiment I.

Dog - 12.5 kg.

(A) Control experiment without administration of
pituitary extract.

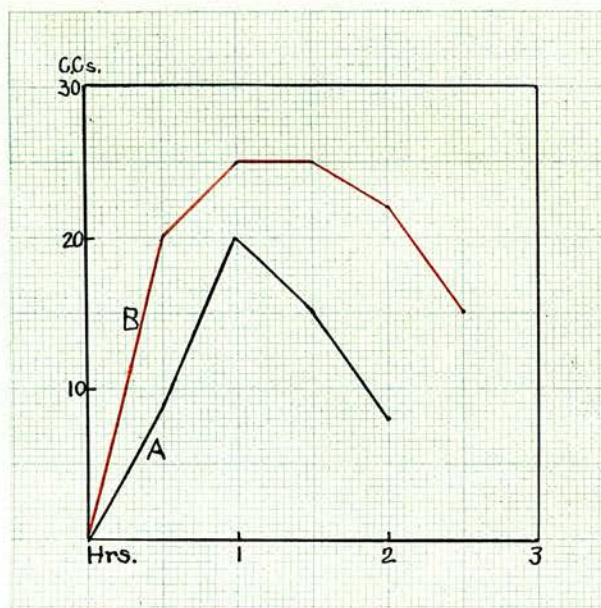
10.15 a.m. Animal catheterised
10.40 " The dissection described above was carried
out under a local anaesthetic (4%
novocain)
11-11.10 " 120 c.c. sterilised Ringer solution given
intravenously
11.20 " Animal catheterised - 9 c.c. urine
11.50 " " 20 c.c. . "
12.20 p.m. " 15 c.c. "
12.50 " " 8 c.c. "

(B) Experiment performed under the same conditions,
but with the administration of pituitary
extract subcutaneously.

10.45 a.m. Animal catheterised
10.50 " 5 mg. pituitary extract in 2 c.c. saline
solution subcutaneously.
10.50-11 " Dissection carried out
11-11.10 " 120 c.c. Ringer solution intravenously
11.15 " Animal catheterised - 20 c.c. urine
11.45 " " 25 c.c. "
12.15 p.m. " 25 c.c. "
12.45 " " 22 c.c. "
1.15 " " 15 c.c. "

Chart XIV./

Chart XIV.



Ordinate = c.c. of urine passed per half-hour period.

Abscissa = Time in hours

Curve A = Normal Diuresis

Curve B = Effect of pituitary extract upon diuresis curve

The intravenous injection commenced at zero -
120 c.c. of Ringer solution were administered
in 10 minutes.

Experiment II. Dog - 15.5 kg.

Part(B) was repeated on another animal.

10.30 a.m. Animal catheterised

10.45 " 5 mg. pituitary extract subcutaneously
in 2 c.c. saline solution.

10.45-10.55 Dissection carried out.

10.55-11.5 120 c.c. Ringer solution intravenously.

11.5 Animal catheterised - 12 c.c. urine

11.35 " 20 c.c. "

12.5 " 24 c.c. "

12.35 " 30 c.c. "

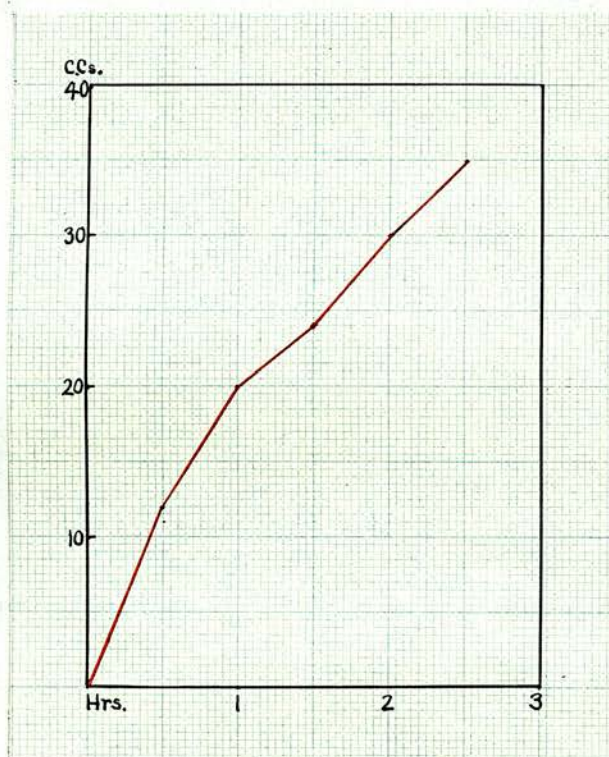
1.5 " 35 c.c. "

In/

In both experiments after the administration of pituitary extract a plentiful diuresis was obtained. In Experiment I. this diuresis was greater than the control diuresis.

The fluid in these experiments was given very rapidly and it was thought possible that this might give a fallacious result by causing a rapid dilution of the blood colloids.

Chart XV.



Ordinate = c.c. of urine passed per half-hour period.

Abscissa = Time in hours

5 mg. of pituitary extract (2 c.c.) administered subcutaneously 15 minutes before zero.

The intravenous administration commenced at zero - 120 c.c.

120 c.c. of Ringer solution were administered in 10 minutes.

Slow/

Slow Transfusion Experiments.

In these experiments 120 c.c. of Ringer solution were administered intravenously during a period of 30 minutes - 4 c.c. per minute. A constant watch was kept upon the burette in order to ensure that the administration was uniform.

The dissection and methods were the same as in the preceding experiments.

Experiment III.

(A) Control Experiment. Without administration of pituitary extract.

Dog - 14.5 kg.

11.50 a.m. Animal catheterised

11.50-12.5 Dissection carried out

12.5 -12.35 120 c.c. Ringer solution administered intravenously.

12.40	Animal catheterised -	5 c.c. urine
1.10	"	6 c.c. "
1.40	"	8 c.c. "
2.10	"	20 c.c. "
2.40	"	10 c.c. "
3.10	"	27c .c. "
3.40	"	16 c.c. "
4.10	"	15 c.c. "
4.40		12 "

(B) /



Experiment III contd.

(B) Experiment repeated under the same conditions
(on another day) but with the administration
of pituitary extract subcutaneously.

10.40 a.m. 5 mg. pituitary extract (2 c.c.) sub-
cutaneously

10.45 " Animal catheterised

10.45-10.55 Dissection carried out

10.55-11.25 120 c.c. Ringer solution intravenously

11.25 Animal catheterised - 13 c.c. urine

12. " 13 c.c. "

12.30 " 10 c.c. "

1.0 " 10 c.c. "

1.30 " 7 c.c. "

2.0 " 10 c.c. "

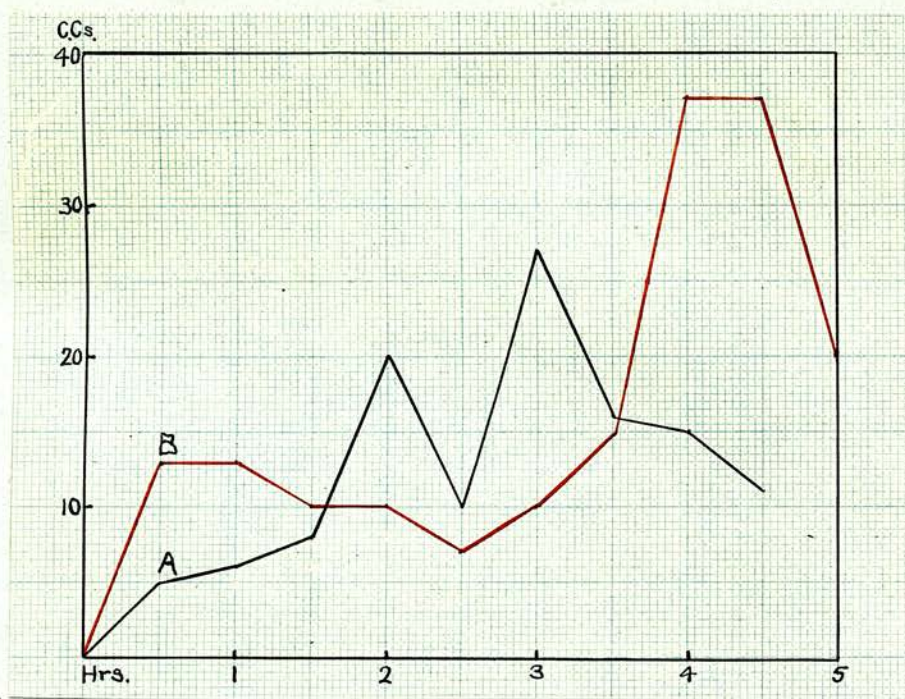
2.30 " 15 c.c. "

3.30 " 75 c.c. = 37.5 per $\frac{1}{2}$ hour

4.0 " 20 c.c.

Chart XVI /

Chart XVI.



Ordinate = c.c. of urine passed per half-hour period

Abscissa = Time in hours

A = Normal diuresis curve

B = Effect of pituitary extract upon normal curve.

The intravenous injection commenced at zero -
120 c.c. of Ringer solution were administered
in 30 minutes.

In curve B 5 mg. of pituitary extract (2 c.c.)
were administered subcutaneously 15 minutes
before zero.

Experiment IV.

Dog - 12 kg.

This experiment was repeated under the same
conditions as Experiment III.

(A) /

Experiment IV.

(A) Control experiment, without pituitary extract.

11 a.m. Animal catheterised.

11.45-11.20 Dissection carried out

11.20- 12 120 c.c. Ringer solution intravenously

12.0 Animal catheterised - 22 c.c. = 11 c.c.
per $\frac{1}{2}$ hr.

12.30 " 9 c.c. urine

1.0 " 6 c.c. "

1.30 " 6 c.c. "

2.0 " 8 c.c. "

2.30 " 10 c.c. "

3.0 " 10 c.c. "

3.30 " 6 c.c. "

4.0 " 5 c.c. "

4.45 " 4 c.c. "
= 3 c.c. per $\frac{1}{2}$ hr.

(B) Experiment repeated under the same conditions as
(A) but with the administration of 5 mg.
pituitary extract subcutaneously.

10.30 /

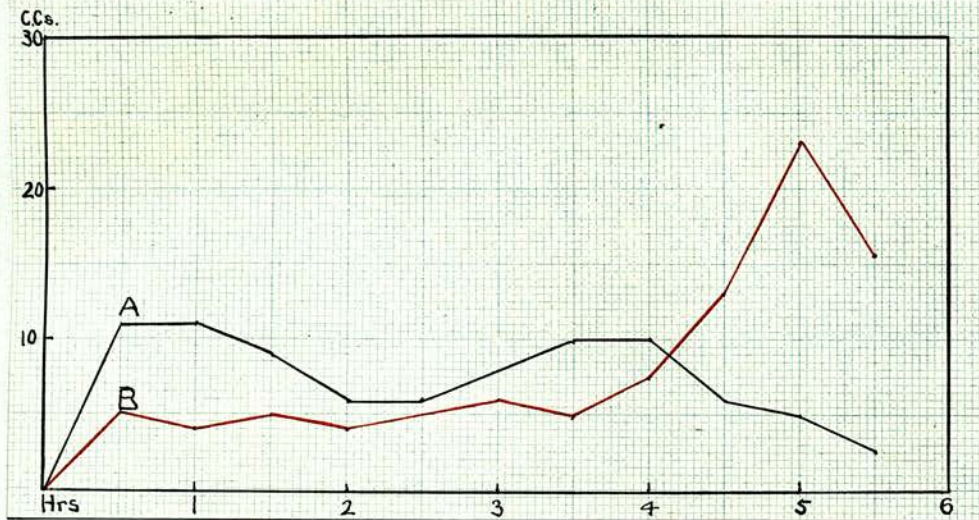
Experiment IV.

Part (B)

10.30 a.m.	5 mg. pituitary extract in 2 c.c. saline subcutaneously
10.45 "	Animal catheterised
10.45- 11	Dissection carried out
11 - 11.30	120 c.c. Ringer solution intravenously
11.35	Animal catheterised - 9 c.c. = 5 c.c. per $\frac{1}{2}$ hr.
12.5	" 4 c.c.
12.35	" 5 c.c.
1.5	" 4 c.c.
1.35	" 5 c.c.
2.5	" 6 c.c.
2.35	" 5 c.c.
3.5	" 8 c.c.
3.35	" 13 c.c.
4.5	" 23 c.c.
4.35	" 15 c.c.

Chart XVII. /

Chart XVII.



Ordinate = c.c. of urine passed per half-hour period

Abscissa = Time in hours

A = Normal diuresis curve

B = Effect of pituitary extract upon normal curve.

The intravenous injection commenced at zero -
120 c.c. of Ringer solution were administered
in 30 minutes.

In curve B 5 mg. of pituitary extract (2 c.c.)
were administered subcutaneously **30** minutes
before zero.

In the control experiments an increased output of urine occurred during the first three hours after the intravenous administration of Ringer solution. When the experiments were repeated with the addition of a subcutaneous injection of pituitary extract the output/

output of urine did not increase appreciably until after $3\frac{1}{2}$ hours when a definite diuresis occurred.

The curves in these experiments do not show the regular form of the diuresis produced by giving fluid by the mouth, but this is not surprising, when it is considered that only 120 c.c. of Ringer solution were administered; to have given more would have necessitated a prolongation of the period of administration, which was found to be impracticable.

In spite of the irregularity of the curves a definite delay in the onset of the diuresis after pituitary extract administration can be made out.

Conclusions:

(1) Pituitary extract causes a delay in the onset of a diuresis produced by giving 120 c.c. of Ringer solution intravenously at the rate of 4 c.c. per minute.

(2) Pituitary extract does not cause a delay in the diuresis if the intravenous administration is given more rapidly - 120 c.c. in 10 minutes.

The Action of Pituitary Extract upon Blood

Composition.

In 1922 Weir, Larson and Rowntree (26) reported that increase of blood volume was not an essential accompaniment of the delayed diuresis resulting from the administration of pituitary extract. They used the Vital Red method of estimating blood volume. In interpreting these results it must be remembered that sufficient time must elapse between blood volume estimations to allow the dye to be eliminated. As a result of this only one estimation can be made each day, and it is possible therefore that an increase of volume may be missed.

In 1923 Underhill and Pack (29) obtained a reduction in the haemoglobin percentage in dogs after the injection of pituitary extract without the administration of water by the mouth. In one case recorded the haemoglobin readings fell from 98 to 80 p.c. one hour after the intravenous injection of the extract, and coincident with this a slight increase in the output of urine occurred. The experiment was open to the fallacy that the blood was taken from an incision in the ear of the animal and not from the interior of a vein.

In 1924 Molitor and Pick (22) investigated the course of the hydraemia during the antidiuresis produced by the injection of pituitary extract; red blood/

blood corpuscle counts and refractometer observations were made. In one experiment they claimed to have produced a reduction in the red blood corpuscle count of over 40 per cent. as a result of giving 500 c.c. of water by the mouth and a subcutaneous injection of pituitary extract. A result such as this would tend to show that the methods were unsatisfactory.

Dr White of the Department of Therapeutics and myself have carried out a series of experiments upon this subject. Acting upon the advice of Professor Meakins, haemoglobin readings were taken as the index of blood volume.

The Haldane haemoglobinometer was used, and the error of the method was checked by Dr White by blood gas analysis and found to be not more than 2 per cent.

Method.

Human beings were used for the experiments. At 8 a.m. a light breakfast was taken; two hours later 2 c.c. of blood were taken from the Median Basilic vein by venepuncture and drawn into a syringe containing a few crystals of potassium oxalate. This was followed immediately by the subcutaneous injection of 5 mg. of posterior lobe extract (in 2 c.c. of saline solution) and within 15 minutes by the administration of varying quantities of water by the mouth.

A sample of blood was taken at hourly intervals thereafter.

Experiment I. /

Experiment I.

Male - 64 kg.

8 a.m. Breakfast

9.55 " First blood sample taken:

	Reading I.	II.	III.
Haemoglobin p.c.	93.5	94	94

10.0 " 5 mg. pituitary extract (2 c.c.)
subcutaneously

10.5-10.25 1500c.c. of tap water taken per os.

11.0 2nd blood sample taken:

	Reading I.	II.	III.
Haemoglobin p.c.	93.5	94	93

12.0 3rd blood sample taken:

	I.	II.	III.
Haemoglobin p.c.	88	86	86

1.0 4th blood sample taken:

	I.	II.	III.
Haemoglobin p.c.	89	89	89

In this experiment no alteration in the haemoglobin readings occurred during the first hour; during the second hour a reduction from 94 per cent. to 87 per cent. occurred and during the third hour there was a rise from 87 per cent. to 89 per cent. In spite of the large quantity of water drunk, no urine was passed until 1.30 p.m., when a profuse diuresis commenced.

Experiment II. /

Experiment II.

Female, 37 years. 34 kg.

8 a.m.	Light breakfast			
10.40	1st blood sample taken:			
		I.	II.	III.
	Haemoglobin p.c.	63	64	64
10.45	5 mg. of pituitary extract subcutaneously (2 c.c.)			
10.50-11	580 c.c. of tap water given by mouth			
12.0	2nd blood sample			
		I.	II.	III.
	Haemoglobin p.c.	58	58	
1.0	3rd blood sample:			
		I.	II.	
	Haemoglobin p.c.	63	63	

In this experiment a reduction of 6 per cent. occurred in the haemoglobin during the first hour after the water was administered; at the end of the second hour the haemoglobin had risen to its normal level.

Experiment III. /

Experiment III.

Female, 30 years. 42 kg.

8 a.m.	Breakfast		
11.0	1st blood sample taken:	I.	II.
	Haemoglobin p.c.	88	88
11.5	5 mg. pituitary extract subcutaneously (2 c.c.)		
11.10- 11.20	870 c.c. of water by the mouth		
12.0	2nd blood sample taken:	I.	II.
	Haemoglobin p.c.	82	82
1.0	3rd blood sample taken:	I.	II.
	Haemoglobin p.c.	84	84

Experiment IV.

Female. 55 kg.

8 a.m.	Breakfast			
10.35	1st blood sample taken:	I.	II.	III.
	Haemoglobin p.c.	88	89	88
10.40	5 mg. pituitary extract (2 c.c.) subcutaneously			
10.40-10.50	800 c.c. of water by the mouth			
11.45	2nd blood sample taken:	I.	II.	III.
	Haemoglobin p.c.	82	82	83
12.45	3rd blood sample taken:	I.	II.	III.
	Haemoglobin p.c.	84	84	84

Experiment V. /

Experiment V.

Male - 70 kg.

8	a.m.	Breakfast		
9.15	"	1st blood sample taken:		
		Haemoglobin p.c.	I. 80	II. 80
9.25	"	5 mg. pituitary extract (3 c.c.) subcutaneously.		
9.30	"	1300 c.c. of water by mouth		
10.20	"	2nd blood sample taken:		
		Haemoglobin p.c.	I. 74	II. 75
11.20	"	3rd blood sample taken:		
		Haemoglobin p.c.	I. 75	II. 75
12.20	p.m.	4th blood sample taken:		
		Haemoglobin	I. 76	II. 75

In all these experiments a reduction of at least 5 per cent. occurred in the haemoglobin readings within the first two hours of the experiment.

Two control experiments were performed in which large quantities of water were taken by the mouth but pituitary extract was not administered.

Experiment VI. /

Experiment VI. Control.

Male - 64 kg.

8 a.m.	Breakfast		
10.50 "	1st blood sample taken:		
	Haemoglobin p.c.	I. 100	II. 101
10.55 - 11.15	1320 c.c. of water given by mouth.		
12.0	2nd blood sample taken.		
	Haemoglobin p.c.	I. 100	II. 100
1.0	3rd blood sample taken.		
	Haemoglobin p.c.	I. 101	II. 101

Experiment VII. Control.

Male - 70 kg.

8 a.m.	Breakfast		
9.50 "	1st blood sample taken:		
	Haemoglobin p.c.	I. 77	II. 76
9.55- 10.10	1300 c.c. of water by mouth		
10.55	2nd blood sample taken :		
	Haemoglobin p.c.	I. 75	II. 75.5
11.55	3rd blood sample taken:		
	Haemoglobin p.c.	I. 75.5	II. 76

In both of these experiments no appreciable reduction of the haemoglobin percentage occurred.

This/

This is in accordance with the findings of Haldane and Priestley (24).

Conclusions.

(1) The haemoglobin percentage was not appreciably altered by the drinking of large quantities of water in human beings.

(2) If the drinking of large quantities of water ⁵was immediately preceded by a subcutaneous injection of pituitary extract, a definite reduction in the haemoglobin percentage occurred within the first two hours of the experiment.

The Mechanism involved in the Control of Diuresis
by Pituitary Extract.

Opinions upon this subject are divided.

Abrahamson and Climenko (19) considered that pituitary extract controls the formation of urine by regulating the salt content of the tissues and not by an action upon the kidney; this view is shared by Molitor and Pick (22).

Rees (17) considered that the delay which he demonstrated in the absorption of fluid from the intestine after the administration of pituitary extract was sufficient to account for the control of diuresis; later (18) as a result of further experimentation, he changed his views.

I have shown (page 36) that delayed absorption from the intestine, if it occurs, is insufficient to account for the control of diuresis observed after the subcutaneous injection of pituitary extract.

Motzfeldt (16) investigated the influence of the nervous system upon the antidiuretic action of pituitary extract. By section of the splanchnic nerve in some experiments, and the renal nerves in others, he was led to the conclusion that the anti-diuretic action was brought about through the splanchnic nerve; he admitted, however, that his results were inconstant.

Weir /

Weir, Larson and Rowntree (26) repeated Motzfeldt's experiments on dogs, but came to the conclusion that pituitary extract did not act through the nervous system.

Abel and Geiling (27) considered that the diminution of urinary output depended largely, if not entirely, on the vasomotor action of the drug.

The work I have carried out does not entitle me to pass an opinion as to the mode of action of pituitary extract. The fact, however, that a hydraemia occurs during the first two hours of the antidiuretic periods (page 58) suggests that the action is renal rather than extrarenal.

I wish to thank Professor Cushny for advice on many of the experiments undertaken, also for the use of his dogs, and also Professor Meakins for access to his wards.

SUMMARY.

- I. In anaesthetised animals intravenous administration of pituitary extract produced a definite diuresis in practically all experiments.
Continuous intravenous administration of pituitary extract in 0.9% saline solution produced the same result.
- II. In unanaesthetised dogs pituitary extract administered subcutaneously controlled the diuresis which normally would have resulted from the administration of water or normal saline solution by the mouth. If concentrated saline solution was used, however, a diuresis resulted.
A diuresis produced by drinking 230 c.c. of 5% urea solution was prolonged, but its onset was not delayed by the subcutaneous administration of pituitary extract.
- III. Delay in the absorption of fluid from the alimentary tract, if it occurs after pituitary extract administration, is insufficient to account for a delay in the onset of the diuresis for three and a half hours.
- IV. A subcutaneous injection of pituitary extract controlled a diuresis produced by the intravenous administration of 120 c.c. of Ringer solution at the rate of 4 c.c. per minute; if, however, the intravenous administration was given at the rate of 12 c.c. per minute, no antidiuresis occurred.
- V. /

- V. The haemoglobin percentage in human beings was not appreciably altered by the drinking of large quantities of water. If, however, the drinking of large quantities of water was immediately preceded by a subcutaneous injection of pituitary extract, a definite reduction in the haemoglobin percentage occurred during the first two hours of the experiment.
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